39. (New) The tissue factor of claim 31 wherein the potential proteolysis sites are deleted by replacing the amino acids with glutaminyl or histidyl residues or deleting one of the basic residues.

40. (New) The tissue factor of claim 31 wherein a residue at an N- or O-glycosylation site is substituted or deleted.

41. (New) Recombinant human tissue factor protein comprising an amino acid sequence from amino acid residue one to amino acid residue 219 as provided in Figure 2, wherein the tissue factor protein has activity in a clotting assay with human plasma.

Remarks

Claims 4-6, 8, and 20-41 are pending.

Claims 4, 5, 6, 8, 20, 24, 25, 27, and 29 have been amended. Claims 22, 26 and 30 have been cancelled. Claim 4 is now directed to a purified tissue factor expressed from a nucleotide molecule encoding a tissue having a sequence as shown in Figure 2 or as shown in Figure 2 except that the N- or O- glycosylation site(s) have been modified. Claims 5, 6, and 20 were also amended to define the tissue factor in terms of the tissue factor encoded by the nucleotide molecule from which it is expressed. As discussed below, this encompasses proteins which are post-translationally processed to cleave amino acid one or two from the final product and yet is fully enabled by the specification. The objected to language relating to amino acid three has been deleted. Claim 8 has been amended to recite that the protein of

claim 4 is expressed in a non-human cell. Claims 24 and 25 have been amended into independent form. Claim 27, which was independent, has been amended to depend from claim 20, which is drawn to a soluble (in contrast to purified tissue factor, as defined by claim 4, which could be purified from the cell surface or expressed in soluble form) tissue factor expressed in a recombinant non-human cell, selected from the group named in claim 27.

Claims 31-31 are newly added. Claim 31 encompasses recombinant human tissue factor proteins expressed from a nucleotide sequence encoding an amino acid sequence which includes amino acids 1 to 219 as disclosed in Figure 2. Claim 41 encompasses recombinant human tissue factor proteins which includes amino acids 1 to 219 as disclosed in Figure 2. Support for claims 31 and 41 appears at least on page 6, lines 10-13, and lines 18-27; page 9, lines 12-25; page 13, lines 4-5; from page 13, line 35, to page 14, line 5; Figure 2; and Figure 5. Specific support for the recited amino acid range (from amino acid 1 to amino acid 219) is provided by Figure 5 where this region is depicted as the first open bar, the indication (on page 9) that the filled bar in Figure 5 begins at amino acid residue 220, the disclosure that deletion variants of human tissue factor protein are specifically contemplated (see, for example, page 11, lines 21-23; from page 12, line 31, to page 13, line 16; from page 15, line 19, to page 16, line 5), and the indication that deletion variants of tissue factor protein having substantial portions deleted are specifically contemplated (see, for example,

the first full paragraph of page 13 where varient tissue factor fragments having as few as 100 residues are specifically discussed).

Support for claims 32 and 33 appears at least on page 15, lines 20-27. Support for claim 34 appears at least on page 16, lines 11-13. Support for claim 35 appears at least on pages 19-22, and especially on page 22, lines 11-12. Support for claim 36 appears at least on page 11, lines 21-32; and page 6, lines 24-25. Applicants note that the cited passage on page 6 specifically indicates generic fusions as an alternative to either a methionine fusion or a signal sequence fusion. Support for claim 37 appears at least in the paragraph bridging pages 10 and 11. Support for claims 38-40 appears at least in the first full paragraph on page 16.

Rejections under 35 U.S.C. §112, first paragraph

1. The specification has been objected to, and claims 4-6, 8 and 20-29 have been rejected, under 35 U.S.C. §112, first paragraph, on the basis that the specification, as originally filed, does not provide support for the invention as now claimed. This rejection is respectfully traversed if applied to the amended claims.

The rejection notes that "claim 4 is drawn to a tissue factor variant having 'a least amino acid three to at least amino acid 219'", and asserts that the specification neither describes such a molecule nor provides basis for the quoted phrase. The rejection also notes that "claim 20 is drawn to a molecule that has the sequence from amino acid one, two, or

three to an amino acid between residues 219 and 263", and asserts that the specification does not "teach" that functional tissue factor may begin at residues one, two, or three. The rejection also asserts that the proteins recited in claims 27 and 29 are not disclosed in the specification. The rejection also asserts that the specification discloses tissue factor variants that lack residues 220-243, have "specific" insertions, have "specific" point mutations, or have altered glycosylation sites, concluding that "claims to other variants constitute new matter. These rejections are believed to be mooted by the amendments to the claims.

However, the standard regarding what is or is not supported by the specification has been clearly articulated as requiring the specification to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the invention, i.e., whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 19 USPQ2d 1111, 1117 (Fed . Cir. 1991). In this regard, applicant also directs attention to MPEP § 2163.02 which describes the standard to be applied in determining if the written description requirement is satisfied. MPEP § 2163.02 reads, in pertinent part:

> Whenever the issue [of adequacy of the written description] arises, the fundamental factual inquiry is whether *a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed*. The subject matter of the claim *need not be described literally* (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. (emphasis added)

Applicants initially note that contrary to assertions in the rejection, the specification discloses many more tissue factor variants the four classes listed in the rejection. For

example, numerous deletion variants of tissue factor are disclosed, including deletions "characterized by the removal of one or more amino acid residues from the tissue factor protein sequence" (page 12, lines 31-32), deletions resulting in tissue factor protein fragments of as few as 100 amino acids (page 13, lines 7-16), and deletion of the transmembrane domain (see, for example, page 13, lines 4-5).

Applicants also note that, contrary to assertions in the rejection, the specification clearly conveys that the variant tissue factor proteins contemplated by applicants are not limited to substitutions, insertions, deletions, or altered glycosylation sites in the alternative. For example, on page 11, lines 21-23, the specification state that "amino acid sequence variants of tissue factor protein fall into one *or more* of three classes: substitutional, insertional or deletional variants" (emphasis added). Applicants submit that this clearly conveys that applicants contemplated combinations of the disclosed classes of variants.

Contrary to assertions in the rejection, the specification is not limited to description of specific deletions, specific insertions, and specific substitutions. Each of these classes of variants is described in broad terms to include numerous alterations. Applicants note that the specification indicates that deletions of the transmembrane domain are not considered to be limited to deletion of only those specific amino acids. For example, in the first full paragraph on page 15, the specification states that "a major *class* of substitutional or deletional variants *are those involving* the transmembrane, i.e. hydrophobic or lipophilic,

region of tissue factor protein" (emphasis added). Note the use of the word "class", the reference to plural variants, and the use of the word "involving". Applicants that this sentance clearly conveys that applicants contemplated deletion variants which include both the deletion of the transmembrane region and deletion of other amino acids. Such variants, including deletion of other amino acids, are clearly encompassed by the use of the word "involving". Accordingly, at least this passage, when combined with the general and broad description of deletions in general, clearly indicates that applicants contemplated deletion variants of tissue factor in which both the transmembrane and other C-terminal amino acids are deleted. Deletion variants "involving" both the deletion of the transmembrane region and deletion of other amino acids is also clearly indicated in, for example, the first full paragraph of page 13, where varient tissue factor fragments having as few as 100 residues are specifically discussed.

Applicants also submit that deletions "involving" the transmembrane region (see discussion above) clearly encompass deletions of less than the entire transmembrane region, since a deletion variant in which a part of the transmembrane region is deleted is clearly a deletion "involving" the transmembrane domain. The examiner should note that three groups independently and within three months of each other obtained the gene encoding human tissue factor, determined that the transmembrane region could be deleted and that a truncation could be made at amino acid 219, or shortly thereafter, to yield a soluble protein.

The amino terminus of human tissue factor is naturally cleaved by post-translational processing. This information was independently ascertained and presented by Dr. Ron Bach and Dr. James Morrissey at the Proceedings of the American Heart Association in November 1986, which was cited in the Information Disclosure Statement and cited by the European Patent Office against the corresponding European application. As a result, even though the gene encodes tissue factor which includes a signal peptide and amino acids one to 263, post translational cleavage may occur prior to amino acid one (leaving one through 263), two (leaving two through 263), and three (leaving three through 263). Accordingly, the claimed protein, even though expressed from a nucleotide molecule encoding an amino acid sequence beginning with amino acid one will include tissue factors beginning with anyone of these amino acids.

In the case of the present claims and disclosure, the specification and claims describe human tissue factor protein including numerous alternative variants (see pages 11-16). As noted above, Figure 5 in the application illustrates different domains of the human tissue factor protein. The specific main region of human tissue factor referred to or recited in the claims, amino acid residues 1 to 219, correspond to the domain preceding the transmembrane domain as illustrated in Figure 5. Applicants assert that all of the human tissue factor variants described in the specification, including proteins including amino acids 1 to 219 of mature human tissue factor protein, are described separately, and in the alternative, in the

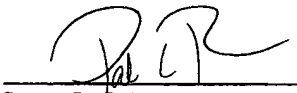
specification. Furthermore, this specific region is illustrated in Figure 5 (see discussion above). As such, it is proper to recite some variants in this group in amended claims. See *In re Driscoll*, 562 F.2d 1245, 195 USPQ 434 (CCPA 1977), where the court criticized a "hypertechnical application" of the description requirement. "In the appealed claim, R is simply alkylsulfonyl (C_1-C_6), whereas in the earlier application, R corresponds to a Markush group of fourteen variable substituents (the R group), one of which is alkylsulfonyl (C_1-C_6)." *Id.* at 1249. Accordingly, applicants assert that the present claims are fully supported by the specification as filed.

2. Claim 30 was rejected under 35 U.S.C. § 112, first paragraph, on the basis that the disclosure is enabling only for claims limited to the disclosed tissue factor fusion proteins. Applicants have previously argued that this rejection is not sustainable and that the claim is fully supported by the specification. However, in order to advance prosecution of this application, claim 30 has been cancelled without prejudice to pursue in a related application.

Serial No: 08/444,934
Filed: May 22, 1995
AMENDMENT AND RESPONSE TO OFFICE ACTION

Allowance of all claims 4-6, 8, 20, 21, 23, 24, 25, 27, 28, 29, and 31-41, is earnestly solicited. All claims as pending upon entry of this amendment are attached in an Appendix to facilitate review by the examiner.

Respectfully submitted,



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Filed: May 22, 1995
AMENDMENT AND RESPONSE TO OFFICE ACTION

Certificate of Mailing under 37 CFR § 1.8(a)

I hereby certify that this Amendment and Response to Office Action, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Patrea Pabst

Date: February 18, 1997

Appendix: Pending Claims:

4. (four times amended) Purified human tissue factor protein expressed from a nucleotide molecule encoding a tissue factor selected from the group consisting of tissue factor having an amino acid sequence as provided in Figure 2 from at least amino acid residue [three] one to at least amino acid residue 219, and human tissue factor having an amino acid sequence as provided in Figure 2 from at least amino acid residue [three] one to at least amino acid residue 219 wherein [a] an amino acid residue at an N- or O-glycosylation site is substituted [or deleted], wherein the tissue factor has activity in a clotting assay with human plasma.

5. (amended) The tissue factor protein of claim 4 wherein the nucleotide molecule does not encode the transmembrane domain [is deleted] defined by amino acids 220 to 243 as provided in Figure 2.

6. (three times amended) The tissue factor protein of claim 4 wherein the nucleotide molecule encodes a tissue factor having an amino acid sequence as provided in Figure 2 from [at least] amino acid residue [three] one to [at least] amino acid residue 219.

8. (three times amended) The tissue factor protein of claim 4 having an amino acid sequence as provided in Figure 2 and expressed in a recombinant non-human host cell.

20. (three times amended) A soluble isolated tissue factor expressed from a nucleotide molecule encoding tissue factor in a recombinant non-human host cell, the tissue factor having [with] the amino acid sequence shown in Figure 2 from amino acid one[, two or three] to an amino acid residue [selected from the group] between amino acid residues 219 [to] and amino acid residue 263, wherein the tissue factor has activity in a clotting assay.

21. The tissue factor of claim 20 which is not glycosylated.

Please cancel claim 22.

23. The tissue factor of claim 20 having an amino acid sequence of Figure 2 from between amino acid one and between residues 220 and 263.

24. (amended) [The] A tissue factor [of claim 20] comprising the amino acid sequence shown in Figure 2 wherein the cysteine residues are substituted with other amino acids.

25. (amended) [The] A tissue factor [of claim 20] comprising the amino acid sequence shown in Figure 2 wherein the potential proteolysis sites are deleted by replacing the amino acids with glutaminyl or histidyl residues or deleting one of the basic residues.

Please cancel claim 26.

27. (amended) [A] The recombinant human tissue factor of claim 20 [comprising the amino acid sequence shown in Figure 2 from amino acid residue three to amino acid residue 219] expressed in a host cell selected from the group consisting of procaryotic cells, non-human animal cells, insect cells, plant cells, and yeast, having activity in a clotting assay.

28. The recombinant human tissue factor of claim 27 which is not glycosylated.

29. (amended) The recombinant human tissue factor of claim 27 comprising the amino acid sequence shown in Figure 2 from amino acid residue [three] one to amino acid residue 263.

Please cancel claim 30.

Please add the following new claims.

31. (New) Recombinant human tissue factor protein expressed from a nucleotide sequence encoding an amino acid sequence comprising from amino acid residue one to amino acid residue 219 as provided in Figure 2, wherein the tissue factor protein has activity in a clotting assay with human plasma.

32. (New) The recombinant human tissue factor protein of claim 31 wherein the nucleotide sequence does not encode the transmembrane domain of human tissue factor.

33. (New) The recombinant human tissue factor protein of claim 32 wherein the nucleotide sequence does not encode the the amino acid sequence from amino acid residue 220 to amino acid residue 243 as provided in Figure 2.

34. (New) The recombinant human tissue factor protein of claim 31 which is not glycosylated.

35. (New) The recombinant human tissue factor protein of claim 31 which is expressed in a host cell selected from the group consisting of procaryotic cells, non-human animal cells, insect cells, plant cells, and yeast.

36. (New) The recombinant human tissue factor protein of claim 31 which includes an amino or carboxyl terminal fusion.

37. (New) The recombinant human tissue factor protein of claim 31 wherein the amino acid sequence consists of from amino acid 1 to amino acid 263 as provided in Figure 2.

38. (New) The tissue factor of claim 31 wherein the cysteine residues are substituted with other amino acids.

39. (New) The tissue factor of claim 31 wherein the potential proteolysis sites are deleted by replacing the amino acids with glutaminyl or histidyl residues or deleting one of the basic residues.

40. (New) The tissue factor of claim 31 wherein a residue at an N- or O-glycosylation site is substituted or deleted.

41. (New) Recombinant human tissue factor protein comprising an amino acid sequence from amino acid residue one to amino acid residue 219 as provided in Figure 2, wherein the tissue factor protein has activity in a clotting assay with human plasma.